

# Lifelong gender health programming in fetal life

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**Summary.** The period from conception to two years of age, and particularly the pregnancy, is crucial for the health of all life. Since lifespan as epidemiology and physiopathology of many common diseases appear different between the sexes, it is very important to know the sex differential contribution to the “developmental origin of health and diseases” during fetal life and also to find more appropriate prevention and diagnostic-therapeutic strategies. Fetal development has growing, metabolic, behavioral sex-specific trajectories and occurs in the mother-placental-fetal system where the fetus and placenta are semiallografts to the mother. The internal and external environmental stimuli are necessary to healthy fetal development and to its adaptive capacities, but if excessive may affect fetal survival chances and increase the life-long risk and susceptibility to cardiovascular, endocrino-metabolic, immunologic, neurologic diseases in a sex specific way. The main biological systems that mediate adaptation to stress are the maternal-placental-fetal neuroendocrine and immune systems, which act according to gender. A more complete knowledge of the adaptation mechanisms, how they act and are integrated with one other might be a mine of preventive and diagnostic-therapeutic instruments.

**Key words:** fetal programming, gender health, stress.

## *Programmazione fetale della salute di genere di tutta la vita*

**Riassunto.** Il periodo dal concepimento ai due anni di età, in un modo particolare la gravidanza, ha un'importanza cruciale per la salute e il benessere di tutta la vita. Poiché la lunghezza della vita così come l'epidemiologia e fisiopatologia di molte comuni malattie sono differenti tra i due sessi, è importante conoscere il diverso contributo dei due sessi all'origine della salute e delle malattie durante la vita fetale anche al fine di più appropriati percorsi diagnostico-terapeutici e di prevenzione. Lo sviluppo embrio-fetale ha differenti traiettorie di crescita, metaboliche, comportamentali sesso-specifiche e avviene all'interno del sistema madre-placenta-feto, dove il feto e la placenta sono semiallogenici rispetto alla madre. La placenta, del sesso del feto, oltre al passaggio di gas e di nutrienti orchestra l'adattamento materno alla gravidanza e la mobilitazione di risorse per il feto, è inoltre una barriera selettiva e ha forte ruolo nella modulazione della speciale immunotolleranza sito-specifica della gravidanza. Gli stimoli ambientali interni ed esterni necessari per un buon sviluppo del feto e delle sue capacità adattative, se sono ec-

cessivi possono dar luogo a una gamma di danni che vanno dalla morte fetale e/o esiti patologici della gravidanza all'aumento del rischio di malattie o di suscettibilità a malattie cardiovascolari, endocrino-metaboliche, neurologiche, immunologiche durante la vita, incidendo anche sulla lunghezza della vita stessa, con diversità tra i sessi. I principali sistemi biologici che mediano l'adattamento allo stress sono i sistemi neuro-endocrino ed immunologico materno-placenta-fetale. Molti casi di stress in gravidanza sono associati a un aumento dei biomarcatori dell'infiammazione e del cortisolo con modalità diverse nel maschio e nella femmina. Conoscere in modo più completo i meccanismi dell'adattamento, le relazioni tra loro e come influiscono nei vari organi e sistemi secondo il sesso può essere una miniera non solo di conoscenze, ma anche di strumenti diagnostici e terapeutici.

**Parole chiave:** programmazione fetale, salute di genere, stress.

## Introduction

Popular experience and “wisdom” as well as evidence of retrospective epidemiological studies indicate that fetal gender may affect pregnancy outcome<sup>1-4</sup>. The male fetal gender is a risk factor for adverse pregnancy outcome, including preterm birth, premature rupture of membranes, gestational diabetes and macrosomia<sup>5</sup>, motor and cognitive outcomes, and a lower likelihood of survival in intensive care<sup>6</sup>.

Moreover over the last two decades it has become increasingly evident how crucial the period from conception to two years of age (the first 1000 days) is for the health and well-being of all life, with special attention to the period of the pregnancy spanning the first 280 days<sup>7</sup>. Since lifespan, as well as epidemiology and physiopathology of many common diseases, appear different between the sexes, it is very important to understand the gender-differential contribution to the “developmental origin of health and diseases” during fetal life, as it is crucial to find more appropriate prevention and diagnostic-therapeutic strategies.

In the last two decades much research has been done into gender health epidemiology and pathophysiology in relation to the pregnancy period, but we need to know

much more, especially about the complex mechanisms that affect the health starting from the embryonal and fetal periods. We are confronted with a mosaic of knowledge relating to fetal health and disease programming with only a few, though very significant, tiles. Research results suggest a complex process with many exogenous and endogenous factors, implicated and related to one other, including gender-specific differences. An excursus of the main areas of knowledge regarding the gender contribution to the developmental fetal origin of non-communicable diseases may help us not only in the orientation of research areas, but also in improving our daily exercise of medical practice.

### The special period of the first 280 days of life

From conception to the birth we experience a special situation in our lives, where:

- the fetal cells are rapidly multiplying and maturing, organizing themselves in different tissues, organs and systems, with their functions and homeostasis, in the process of autonomous development body planning; contemporaneously, the cognitive, emotional, relational and social capacities are developing in an integrated way with the body and its functions. The deep psychological core of each is itself formed during pregnancy.
- this fetal development goes on a sex-specific way. The presence of the Y chromosome conditions the development of the male gonad from the undifferentiated gonad, and the testosterone produced by the male gonad is essential for male fetal development. But sex diversity is also observed in the different origin of the active X chromosome (only maternal in male, with maternal and paternal randomly distributed in the female) and in the gender-differentiated mechanism for X inactivation, with a different pattern of X-linked genes affected, and with an incomplete and definitive deactivation of the second X chromosome: thus an X-linked mutation is expressed in all cells in XY individuals but in only about half of the cells in XX individuals ("mosaicism buffering effect")<sup>8-10</sup>. In genomic studies a transcriptional sexual dimorphism has been observed as well as the fact that some autosomal genes are differently expressed in male and female, starting from the preimplantation period and therefore before gonadic differentiation and steroid hormones secretion<sup>5,11</sup>. So sexual differences concern not only the genital apparatus and the gonadic hormones with their metabolites but also the entire fetus in a complex gender way: different growth, metabolic and temperamental trajectories, different mitochondrial activity, different epigenetic regulation and DNA methylation, different reactions to

environmental stimuli<sup>9</sup>. A complex interaction between chromosomes (sex and autosomal) and sex hormones then drives the sexual dimorphic structural, functional and temperamental development of the fetus. The way the interactions occur may be an intriguing research field.

All of the above happens in the special situation where mother and fetus, genetically diverse and each with its own autonomy, are in a close relationship with each other and both play an obligatory active role in all aspects of development with the placenta interface and mediation (mother-placenta-fetus system). The placenta, of embryonic origin, is the organ for the obligatory and dynamic passage of gases and nutrients to the fetus, and also has many major endocrine functions for orchestrating maternal adaptation to pregnancy and for mobilizing appropriate resources for the fetus; furthermore it is a selective barrier to minimize exposure of the fetus to the maternal hormones such as glucocorticoids, xenobiotics, pathogenic microorganisms, parasites, etc.<sup>12</sup>. The bidirectional placental release of hormones, growth factors, cytokines, etc. into maternal and fetal compartments is a powerful route of communication between the fetus and the mother and profoundly influences both<sup>13</sup>.

The placenta and fetus express both paternal and maternal antigens; they are semi-allografts; the maternal immune system is exposed in pregnancy to paternal antigens expressed by the fetus. A successful pregnancy requires maternal immune tolerance of the fetus and fetal of the mother to prevent inflammation and fetal loss<sup>14</sup>. The immune tolerance, site specific and not systemic, consists in a complex mechanism partially known at cellular, biochemical, hormonal level where the placenta plays a fundamental orchestrating role and acts in a gender-specific way. A maternal anti-fetal rejection can be associated to the development of a fetal systemic inflammatory response and it is significantly associated with the great obstetrics syndromes such as preterm and term fetal growth restriction, spontaneous preterm delivery, small size for gestational age associated with pre-eclampsia, fetal death<sup>15-16</sup>.

The placenta is of the same genotype as the fetus and there is some evidence that its development and its functions are sexually dimorphic. The fetus and the placenta work in the same gender way, cooperating in the specific developmental trajectories: male fetuses are larger than female fetuses at birth, they invest resources in growth, they do not adapt to maternal conditions, while female fetuses do not invest all resources in growth, but also in placental growth, conserving resources as glycogen and adjusting to maternal conditions in multiple ways<sup>5</sup>. As a result, for example, male fetuses when faced with adversity have less probability of survival than females; females adjust to adversities with a variety of strategies,

but their escape from the risk of early mortality or morbidity pays the price of increased vulnerability expressed later in the development and during the lifetime<sup>17</sup>.

As in the fetus, the sex biased placental genes expression are distributed in all chromosomes, the majority in autosomal chromosomes<sup>18</sup>. The placental transcripts (beta HCG, epidermal growth factor, insulin-like growth factor, cytokine, CRH, etc. ) are expressed in a sexually dimorphic manner<sup>13,19</sup>. In the global transcriptomic profile of human placenta females possess more up-regulated autosomal genes, including immune regulating genes, than males<sup>18</sup>. Male-specific Y linked genes encode epitopes that contribute to the H-Y antigen acting as minor histocompatibility antigen<sup>20</sup>; male biased genes are also enriched in genes related to the immune and inflammatory system<sup>18,21</sup>. Female placentas tend to have higher expression of genes involved in immune regulation, endocrine functions and placental growth<sup>18,22</sup>, while male placentas have more inflammatory profiles<sup>23</sup>. In disorders of pregnancy immunologic balance, male foetuses seem to be less favourably placed.

### Sex fetal programming and gender ways in developmental origin of health and diseases

The embryo-fetal-placental development is a plastic process where a single genotype can express many different phenotypes. Developmental processes from genotype to phenotype occur in a context-dependent way. During sensitive periods of cell proliferation, differentiation, organization and maturation the embryo and the fetus respond to the conditions of the internal and external environment with structural and functional adaptive changes at the cellular, tissue and organ system levels. In the biological plastic processes related to maternal stress action on the fetal development, all the mother-placenta-fetus system is involved in an integrated manner where every part plays a triple role as sensor, transducer and effector<sup>24-25</sup>.

Although internal and external environmental stimuli are necessary for healthy structural and functional fetal development, as throughout the whole lifetime, excessive stressors may not only affect the fetal survival possibilities and increase the risk of pathologic outcome of pregnancy but may also increase the risk of disease and susceptibility to disease during the individual's lifetime and may have an effect on the lifespan itself.

In the 1980s epidemiologist David Barker observed an inverse relationship between birth weight and death for ischemic heart disease in adulthood; he also observed that these deaths had the same geographical (low resources and poor social conditions areas) distribution of neonatal death as about 60 years before. He assumed that neonatal deaths and precocious ischemic heart death

increased risk in adulthood may have the same origin in restrictions during intrauterine life. In spite of initial scepticism, Barker's observations have been confirmed not only by other more than five hundred studies conducted by Barker himself, but also by studies conducted by many other authors in many other countries, also when considering many other health aspects related to cardiovascular, immunologic, metabolic, neurologic systems and also ageing and lifespan or cancer risk<sup>26-30</sup>.

The birth weight almost always correlates to placental weight, but also to some placental efficiency morphologic indicators as observed in different placental phenotypes<sup>31</sup>. In a study of 13345 men and women born in 1934-1944 (Helsinki Birth Cohort) hypertension and hypertension treatment were associated with low placental weight<sup>32</sup>; and in men who were exposed in utero to starvation during the post-war famine in Holland, the surface area and the shape of placenta predicted hypertension<sup>33-34</sup>. Numerous studies have shown a relationship between small placenta and/or its phenotypes expressing undernutrition/hypoxic complications and increased risk of heart failure<sup>35</sup>, coronary heart disease especially in men<sup>36</sup>, sudden cardiac death in adulthood<sup>37</sup>, increased insulin resistance<sup>35</sup>, diabetes<sup>37-38</sup>, asthma<sup>39</sup>, affective and cognitive disorders<sup>40</sup>.

Low birth weight, like low placental weight, may be a frequent phenotype of an altered fetal growth due to different causes such as low uterine blood supply and placental insufficiency or failure but also to the mother's under-nutrition or malnutrition, abnormal mother body composition, parental alcohol abuse, parental smoking, exposure to pollutants, to psychosocial stressors. These types of stressors may act in an isolated way but more often in the same situation many types of stressors may be acting together<sup>41</sup>.

Many retrospective studies have observed relations between prenatal stress and an increased risk of a poor pregnancy and/or poor neonatal and children outcomes such as a reduction in gestational length, intrauterine growth restriction but also language retardation and affective, cognitive disorders or schizophrenia in women exposed to traumatic events such as severe earthquakes<sup>42</sup>, ice storms<sup>43</sup>, flooding<sup>44</sup>, war<sup>45</sup>, a terrorist atrocity<sup>46-47</sup>. Retrospective studies however are faced with the difficulties of defining the stressor entity in the extent or the timing of mother exposure, and many other variables associated to the event, so prospective studies have been planned.

In the Ice Storm project in Quebec the objective and subjective stress intensity level was assessed and compared with outcomes and other variables such as age, fetal sex, period of pregnancy during exposure. The stressful events were acting independently of other factors, but exposure timing, fetal sex and type of stressor influenced the effects observed<sup>48</sup>; following the cognitive, behavioural, motor and physical development of children exposed in uterus

to the 1998 Quebec Ice Storm the objective grade of exposure and the mother's subjective stress have a strong and persistent effect on child development and these effects were often moderated by the timing of the exposure during pregnancy and by the child's sex<sup>49</sup>. In a population-based cohort study of 5.3 million children followed up to 37 years of age in births from women who suffered a severe prenatal bereavement during the pregnancy, a 10% increase in long-term natural mortality risk was observed for all causes, but greater in endocrine, metabolic, nutritional diseases and nervous system diseases<sup>50</sup>, and increased alimentary disorders, especially in male births<sup>51</sup>. In a review of nineteen studies, intimate partner violence during pregnancy was associated with an increased risk of preterm birth and low birth weight<sup>52</sup>. In births to mothers suffering from high degrees of anxiety during pregnancy, the following was observed at birth: low weight, reduced cranial circumference, increased risk of preterm birth, etc. and in childhood: increased risk of both emotional problems such as hyperactivity, attention problems, higher levels of impulsivity and reaction to novelties, and of cognitive problems such as learning delay, academic delay, laterality or other neurodevelopment disorders. Some studies have shown a distribution of sex-specific psychopathological outcomes<sup>40</sup>.

Experimental prospective studies in mammals on the effect of many types of programmed stressors have evidenced structural impacts in growth-restricted fetus as a lower endowment of cardiomyocytes and a higher proportion of mononucleated (immature) cardiomyocytes<sup>53-54</sup>, as well as less elastin in the arteries<sup>55</sup>; moreover in these restricted offspring a lower number of cells has been observed in key organs, such as nephrons in the kidney<sup>56</sup> or insulin producing beta cells in the pancreas<sup>57</sup>, together with an impairment of the structure and maturation of the lung<sup>58</sup>, the liver<sup>59</sup> and the brain<sup>60</sup>. Other experimental studies on animals suggest that maternal exposure to stressors in pregnancy may simultaneously affect several physiological systems in offspring and the extent of prenatal stress can produce long-term effects, altering or not the birth phenotype<sup>61-62</sup>.

Nevertheless also in a stress exposed, non-growth restricted fetus it is possible to find functional alterations. Entringer S designed and implemented some retrospective case-control studies in young adults born after a seemingly healthy pregnancy but exposed during their intrauterine life to psychosocial stress, and found pre-disease markers of physiological dysregulation of metabolic, endocrine and the immune system as early predictors of disease susceptibility. The stress-exposed group exhibited: higher BMI and body fat percentage, primary insulin resistance, and a lipid profile consistent with the metabolic syndrome; altered immune function with Th2 shift in the Th1/Th2 balance, consistent with increased risk of asthma and autoimmune disorders;

altered endocrine function, with an increased ACTH and reduced cortisol levels during pharmacological and psychological stimulation paradigms, an impaired prefrontal cortex related to cognitive performance (impairments in working memory performance after hydrocortisone administration<sup>63-65</sup>).

The frequent association of biological and psychological alterations in fetal programming poses intriguing questions.

The fetal brain is highly plastic; in order to develop it is not only receptive but needs signals and stimuli from its environment. During the long ontogenesis of the brain from the fetal period to adolescence, the fetal period is particularly important because the growth and differentiation of the major brain structures, as well as the gender differentiation, take place with the mandatory critical role of endocrine and immunological mediators of the mother-placenta-fetus system in many important aspects of brain development, including migration of neuronal and glial cells, differentiation, synaptic maturation; inappropriate levels of these biological mediators can produce harmful effects on the developing brain<sup>66</sup>. Even small and delicate changes in brain structure and function during fetal life can be progressively and substantially amplified over time, producing lasting or permanent deficits. In epidemiological studies there is substantial empirical evidence that exposure to excessive stress during fetal life may result in negative outcomes of both short-term and long-term neurodevelopment<sup>67</sup>.

Growth restricted fetus with chronic hypoxia, hypoglycaemia, oxidative stress and inflammation are more likely to present in postnatal life neurodevelopmental disorders and subclinical psychosocial problems. In obstetrics and neonatology the phenomenon of "brain sparing" is well known, and is a modification of fetal circulation to safeguard as far as possible the brain structure and function during hypoxia or nutritive restriction. Brain sparing in the first phase involves vasodilatation in the anterior cerebral artery and when the hypoxia becomes more severe the brain perfusion shifts to favour deep grey matter with the middle cerebral artery dilatation. The outcomes of brain sparing are an elevated brain/body weight ratio, asymmetric growth, but also reduced white matter, delayed myelination and functional deficit which can result in abnormal behaviour, attention deficit, low IQ, impaired motor abilities. So brain sparing is a partial protective strategy and while it is a useful indicator of the grade of impairment, it does not ensure normal brain development<sup>68-69</sup>.

Many studies on fetal brain programming are carried out on animals, only a few recent studies are in humans. New non-invasive technical possibilities of examining the brain have opened up new research horizons. The duration (even after 37 weeks) of pregnancy is positively correlated with the development of gray matter<sup>70</sup> and

with the efficiency of the brain network in the average childhood<sup>71</sup>. The children of mothers with high levels of anxiety in the 2nd trimester of pregnancy had a reduction of functions<sup>72</sup>. The seven-year-old children of mothers with depression during pregnancy showed a reduction in cortical thickness of the right frontal lobe and there was a significant association with deviant behaviour<sup>73</sup>. Sex-differentiated brain developmental trajectories, neuronal circuits organization and responses to stress during fetal period may be linked with a different vulnerability to mental health problems. Many studies indicate a sexually dimorphic response to early life stress: greater prevalence of affective problems in females and greater prevalence of autism spectrum disorders in males<sup>74</sup>.

Another intriguing suggestion comes from a number of relevant epidemiologic comorbidities that occur in a sexually dimorphic way. Women have also twice as much risk of major depressive disorders associated with cardiovascular disease and/or with obesity and metabolic syndrome. These frequent comorbidities seem to share some anatomical and molecular substrates. The cortical and subcortical brain regions involved in stress circuitry that regulate mood, metabolic functions and the autonomic nervous system are the more sexually dimorphic. In women brain regions appearing larger in volume, related to the size of the cerebrum, are the orbitofrontal cortex, anterior cingulate cortex and hippocampus, whereas in men these are the amygdala and hypothalamus<sup>75</sup>. The same regions have dense sexually dimorphic distribution of receptors of gonadal and adrenal hormones and of peptides implicated in hunger and satiety regulation such as ghrelin and leptin. Stressor impact, particularly during the sexual differentiation of the fetal brain, might explicate the sexually different frequency of these comorbidities<sup>76-77</sup>.

Excessive stress during pregnancy may lead to an increasing risk of a wide range of pathologic pregnancy outcomes including fetal death, fetal developmental impairment, diseases or susceptibility to diseases in adulthood of cardiovascular, endocrine-metabolic, neurological, immunological systems, shortened lifespan, even transmissible to the next generations<sup>78</sup>. The type and the extent of the damage, as the association of more than one type of damage may be in relation with both the genotype and the entity and the length of the stress, the developmental stage of the fetus and of the placenta, the ability of that fetus-placenta-mother system specific type in that situation to react to stressors; there is also an important role of the fetal-placental sex.

Many different factors contribute to the fetal developmental plasticity with different outcomes, but the impact on the structural and functional integrity and survival of the organism seems to be traceable back to two fundamental and interlinked processes, substrate availability (oxygen, nutrition) and intrauterine envi-

ronmental stimuli (stress)<sup>79</sup>. Experimental nutritional manipulations in animals, particularly in preconception or early pregnancy, may affect maternal and fetal outcomes via alterations in stress biology (cortisol, inflammatory cytokines)<sup>80-81</sup> in the same way as in animal and human stress induction may act on feeding behaviour, food choices, and the fate of food metabolism in target tissue<sup>82-83</sup>. Growing evidence supports the concept of a bidirectional interaction between nutrition and stress, indicating that the effect of nutrition on health may vary as a function of stress, or the effect of stress on health may vary as a function of nutritional status<sup>25</sup>.

### Mechanisms of fetal programming by prenatal stress: looking for gender ways

Thousands of studies describe many different effects of different stressors on the pregnancy outcomes and on the offspring health up to the adulthood. Different stressors from poverty, famine, man-made or other disasters, to bereavements, violence, anxiety, depression and alcoholism, drug abuse, pollutions etc. may have the same type of effects or the same stressor may have different effects on different organs and systems, influenced by many types of variables, not least the placental-fetal sex.

The adaptation to stress in the developing fetus is a complex process that is not completely understood, where many mechanisms are involved and integrated with one other; there is substantial agreement that the main biological systems that mediate adaptation to stress are the maternal-placental-fetal, neuroendocrine and immune systems<sup>25,84</sup>. There is still much to learn about how these systems act and how they may be related.

Inflammation typical of maternal anti-fetal rejection is significantly present in the great obstetrics syndromes often associated with an impaired immunological balance<sup>16</sup>. Elevated levels of placental inflammation have been observed in slower postnatal growth in preterm infants<sup>85</sup>. In animals prenatal exposure to the inflammatory cytokine interleukin-6 (IL-6) programs for hypertension associated with alterations of renin-angiotensin system and of sodium excretion in the offspring<sup>86</sup>. Major Depressive Disorders in pregnancy are associated with increased inflammation biomarkers such as IL-6, TNF $\alpha$ , vascular endothelial growth factor together with elevated cortisol levels and altered offspring behavior<sup>87</sup>.

Many studies both in animals and in humans examine the maternal endocrine stress axis during pregnancy and the effects of its activation on the physiological and psychological outcomes in births<sup>40,88,89</sup>. During pregnancy the synthesis and release of pituitary peptides in the mother increases and hormone production from target tissue as cortisol from adrenal gland also increases.

Corticotropin Releasing Hormone (CRH) participates as an autocrine and paracrine modulator in various reproductive functions that have an inflammatory component from the ovulation and luteolysis, to the blastocyst implantation and the immunological tolerance equilibrium in the mother-placental-fetal system and as a clock in the timing of the delivery<sup>90</sup>. The placenta is the key modulator of signals coming from the mother before they are transduced to the embryo-fetus and vice versa and therefore it is the primary factor responsible for the profound changes in the maternal/fetal stress system<sup>13</sup>. Placenta expresses genes for CRH from the seventh week with a progressive increase, which becomes exponential in the latter part of pregnancy; placental CRH is identical to the hypothalamic CRH, but maternal stress signals such as cortisol activate a placental CRH positive feedback in contrast with the negative feedback with the hypothalamic CRH<sup>73</sup>.

Cortisol is one of the main biomarkers of stress due to the fact that its production, bioavailability and activity is altered in all conditions that have shown the ability to program fetal development<sup>91</sup>. Glucocorticoids are an important switch driving the gene regulation changes in fetal normal growth and maturation<sup>92</sup>. The concentration of serum glucocorticoids in the fetus is low throughout most of the gestation but surges in the week prior to birth, when together with CRH, they are an important developmental switch leading to fundamental gene changes for the organ and system maturation in the transition to postnatal life<sup>93-94</sup>.

In animal experimental studies fetal exposure to glucocorticoid excess induces restricted growth<sup>95</sup>, programs blood pressure increase<sup>96-97</sup>, reduction in nephron number, and alters renal gene expression in the fetal spiny mouse<sup>98</sup>, impaired vascular function indicating an effect on fetal organs and system development<sup>91</sup>. Disruptions in the timing or sequence of organ development, with tissue remodeling, can result in producing smaller organs or altered organ morphology and/or function, while also modifying the physiological capacity of the organ throughout the lifespan, with a negative influence on health and disease<sup>73</sup>.

The direct exposure of the fetus to the maternal cortisol is regulated by the placental 11 beta-hydroxysteroid-dihydrogenase type 2 (11beta HSD2) which oxidizes the cortisol to the inactive form (cortisone), but it is a partial barrier; 11beta HSD2 activity is downregulated by high levels of maternal anxiety<sup>99</sup>, serious infections<sup>100</sup>, high levels of pro-inflammatory cytokines<sup>101</sup>, alcohol exposure<sup>102</sup>, and this downregulation is observed in the placentas of pregnancies complicated by preeclampsia<sup>103</sup> and intrauterine growth restriction<sup>104</sup>.

In adult men and women low birthweight is associated with high fasting cortisol levels with increased cortisol responses to stimulation with hexogen ACTH or to

stress<sup>105</sup> indicating a long-term programming of hypothalamic-pituitary adrenal function<sup>93</sup>. A dysregulation of the maternal hypothalamic-pituitary-adrenal axis with elevated glucocorticoid and inflammatory expression may impact the fetal hypothalamic-pituitary-adrenal in sex-dependent ways<sup>77</sup>.

Fetal glucocorticoid hyper exposure acts through molecular mechanisms that include epigenetic changes in target gene promoters such as glucocorticoids receptors<sup>106</sup>; the altered level of tissue-specific glucocorticoids receptor expression occurs in a sex-differentiated way<sup>107</sup>, may be persistent and profoundly alter glucocorticoid signaling in many organs, predisposing the individual to disease in later life. The epigenetic changes may be also transmitted via the father or mother to the subsequent generations<sup>108-109</sup>.

Maternal cortisol can stimulate and increase the production of placental Corticotrophin Releasing Hormone (CRH) that stimulates fetal adrenal steroid biosynthesis<sup>110-112</sup>. Hyper-responsiveness of the fetal hypothalamus-pituitary-adrenal axis may also involve the activation of the fetal sympathetic nervous system by programming for a greater stress reactivity<sup>113</sup> and increasing cardiovascular risk in later life<sup>106</sup>.

Moreover many studies suggest cortisol as the primary driver of sex differences in fetal and neonatal development and survival; the male and female fetus institute different mechanisms to cope with an adverse environment or event. In response to maternal glucocorticoid exposure, female placenta increases its permeability to maternal glucocorticoids with changes in expression of 11 beta-hydroxysteroid dehydrogenase enzymes, and female offspring have increased HPA axis reactivity compared with males, who provide some evidence of altered diurnal cortisol secretion<sup>114</sup>. In the human fetus, exposure to cortisol early in gestation and to placental CRH at 31 weeks is associated with delayed neuromuscular and motor maturation significantly only among males<sup>12</sup>. The fetal exposure to elevated CRH at 25 gestational weeks is a risk for fearful or reactive temperament in female infants<sup>115</sup>. A rise of maternal cortisol appears to induce in males a state of glucocorticoid resistance, while females remain sensitive to changes in cortisol concentration; the differences may be due also to different combinations of the numerous placental receptors to glucocorticoids in the different sexes<sup>107</sup>.

The cascade of mechanisms activated in the fetal developmental programming as genic expression, DNA methylation and epigenetic way, telomere and mitochondrial biology just like many systems such as the sympathetic nervous system, the renin angiotensin system, oxidative stress, endothelin system and inflammatory cytokines also act in a sex-specific way in the normal and pathological aspects. Sex specificity is genetic but sex steroids have an integrated fundamental role during

fetal life, and after. How the permissive role of testosterone and the protective role of estrogen observed in adulthood may contribute to the complexity of chronic diseases in fetal programming is still a theme of research<sup>116</sup>.

## Perspectives

The increasing body of scientific evidence on fetal programming confirms the “developmental origin of health and disease” in fetal life and also the presence of sex specific differences. The numerous studies on the mechanisms into how an environmental context may produce one or other phenotypes opens up broad research horizons. We need to complete our understanding of the fundamental mechanisms of the adaptation to normal and excessive stress action and of the cascade of events they trigger in the organs and systems. How these mechanisms act in a male or female fetus with differences in developing trajectories and how sex steroids cooperate with the genetic program in driving the sexual dimorphic structural, functional, temperamental development of the fetus and postnatal life may be other interesting research

### Key messages

- The embryo-fetal placental development is a plastic process where a single genotype can express many different phenotypes. Developmental processes from genotype to phenotype occur in a dependent context and in a sex specific way.
- Excessive stressors may not only affect fetal survival possibilities and increase the risk of pathological outcomes of pregnancy but may also increase risk of disease and the susceptibility to disease during lifetime and may act on the lifespan itself.
- Adaptation to stress in the developing fetus is a complex process where many mechanisms are involved and integrated with one other; there is a substantial agreement that the main biological systems mediating adaptation to stress are the maternal-placental-fetal neuroendocrine and immune systems; these systems act in a sex-specific way.
- Glucocorticoids are an important switch driving gene regulation changes in normal fetal growth and maturation. Fetal exposure to glucocorticoids excess induces disruption in organ developments, producing smaller organs or altered organ morphology and functions and influencing lifelong health and diseases
- The cascade of mechanisms activated in fetal developmental programming, such as genic expression, DNA methylation and epigenetics, telomere and mitochondrial biology, as well as many other systems, such as the sympathetic nervous system, the renin angiotensin system, the mother-placenta-fetal immunotolerance system, oxidative stress, endothelin system, inflammatory cytokines, act in a gender-specific way.

topics. It is to be hoped that an understanding of the above might also suggest new diagnostic and therapeutic ways to prevent greater obstetrics syndromes, in order to protect the fetus against abnormal programming, to screen individuals with elevated susceptibility to diseases.

While awaiting fresh knowledge, it is desirable that when faced in postnatal life with cardiovascular, metabolic, immunologic diseases or altered neurodevelopmental outcomes we start inquiring after birthweight and consider gender.

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